

CLAIMS

1. A method of treating a tumor in a subject, which comprises administering to said subject an effective amount of at least one agent that decreases the [GSH]²/[GSSG] ratio in the malignant cells of said tumor, wherein said at least one agent is administered continuously to said patient for a period of time within the range of from about 15 to about 75 hours.
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2. A method according to claim 1 wherein said agent or precursor thereof is selected from the group consisting of β -alanyl cysteamine, arsenic trioxide, ascorbic acid, buthionine sulfoximine, camptothecin, capsaicin, carmustine, daunorubicin, diamide, diethyl maleate, disulfiram, dopamine, doxorubicin, duroquinone, epothilone A, epothilone B, erbstatin, ethacrynic acid, etoposide, gemcitabine, hydrogen peroxide, an isoflavone, α -lipoic acid, mifepristone, oxidized low density lipoprotein (ox-LDL), a polyunsaturated fatty acid (PUFA), propargylglycine, an
10 unsubstituted or partially substituted quinone, N-(4-hydroxyphenyl) retinamide, retinoic acid, staurosporine, a ubiquinone, an α,β -unsaturated aldehyde, and a phenol.
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3. A method according to claim 2 wherein said isoflavone is selected from the group consisting of catechin, daidzein, dicumarol, (-)epicatechin, flavopiridol, genistein, β -lapachone, myricetin and rotenone ; said unsubstituted or partially substituted quinone is selected from the group consisting of anthraquinone, benzoquinone, 2-methylbenzoquinone, 2,6-dimethyl-benzoquinone, 2,5-dimethyl-benzoquinone, 2,3,5-trimethyl-benzoquinone, γ -tocopherolquinone and δ -tocopherolquinone; said α,β -unsaturated aldehyde is selected from the group
20 consisting of cinnamaldehyde and a 4-hydroxy-C₅-C₉-alkenal selected from the group consisting of 4-hydroxy-C₅-C₉-pentenal, 4-hydroxy-C₅-C₉-hexenal, 4-hydroxy-C₅-C₉-heptenal, and 4-hydroxy-C₅-C₉-nonenal; said phenol is selected
25 from the group consisting of curcumin, (-) epigallocatechin-3-gallate, resveratrol, γ -

tocopherol, δ -tocopherol, yakuchinone A, and yakuchinone B; and said ubiquinone is coenzyme Q₁₀.

4. A method according to claim 1 wherein said at least one agent is administered together with a standard chemotherapeutic drug.

5 5. A method of treating a tumor in a subject, which comprises administering to said subject an effective amount of a synergistic combination of at least two agents that decrease the $[GSH]^2/[GSSG]$ ratio in the malignant cells of said tumor, wherein said agents are selected from the classes consisting of:

- (i) an agent that oxidizes GSH, or a precursor thereof;
- 10 (ii) an agent that forms an adduct or a conjugate with GSH, or a precursor thereof;
- (iii) an agent that inhibits the GCS enzyme; and
- (iv) an agent that inhibits the glutathione reductase (GR) enzyme,

15 6. A method according to claim 5 wherein said synergistic combination comprises at least one agent that oxidizes GSH, or a precursor thereof, and at least one agent that forms an adduct or conjugate with GSH, or a precursor thereof.

7. A method according to claim 6 wherein said at least one agent that oxidizes GSH or a precursor thereof is disulfiram, hydrogen peroxide, a precursor thereof 20 selected from the group consisting of ascorbic acid and dopamine, α -lipoic acid, oxidized low density lipoproteins (ox-LDLs), and a quinone selected from the group consisting of duroquinone, an ubiquinone, and β -lapachone, and said at least one agent that forms an adduct or conjugate with GSH, or a precursor thereof, is selected from the group consisting of arsenic trioxide, diethylmaleate, ethacrynic acid, epothilones A and B, an α,β -unsaturated aldehyde, an unsubstituted or 25 partially substituted quinone, an isoflavone, and a phenol.

8. A method according to claim 7 wherein said at least one agent that forms an adduct or conjugate with GSH, or a precursor thereof, is selected from the group consisting of an isoflavone, an unsubstituted or partially substituted quinone, an α,β -unsaturated aldehyde, and a phenol, wherein said isoflavone is selected from
5 the group consisting of catechin, daidzein, dicumarol, (-)epicatechin, flavopiridol, genistein, β -lapachone, myricetin and rotenone ; said unsubstituted or partially substituted quinone is selected from the group consisting of anthraquinone, benzoquinone, 2-methylbenzoquinone, 2,6-dimethyl-benzoquinone, 2,5-dimethyl-benzoquinone, 2,3,5-trimethyl-benzoquinone, γ -tocopherolquinone and δ -
10 tocopherolquinone; said α,β -unsaturated aldehyde is selected from the group consisting of cinnamaldehyde and a 4-hydroxy-C₅-C₉-alkenal selected from the group consisting of 4-hydroxy-C₅-C₉-pentenal, 4-hydroxy-C₅-C₉-hexenal, 4-hydroxy-C₅-C₉-heptenal, and 4-hydroxy-C₅-C₉-nonenal; and said phenol is selected
15 from the group consisting of curcumin, (-) epigallocatechin-3-gallate, resveratrol, γ -tocopherol, δ -tocopherol, yakuchinone A, and yakuchinone B.

9. A method according to claim 7 wherein said synergistic combination comprises disulfiram and diethyl maleate or a quinone.

10. A method according to claim 5 wherein said synergistic combination comprises at least one agent that oxidizes GSH, or a precursor thereof, and at least
20 one agent that inhibits the GCS enzyme.

11. A method according to claim 10 wherein said least one agent that oxidizes GSH or a precursor thereof is disulfiram, hydrogen peroxide, a precursor thereof selected from the group consisting of ascorbic acid and dopamine, α -lipoic acid, oxidized low density lipoproteins (ox-LDLs), and a quinone selected from the group
25 consisting of duroquinone, an ubiquinone, and β -lapachone, and said at least one agent that inhibits the GCS enzyme is buthionine sulfoximine (BSO).

12. A method according to claim 5 wherein said synergistic combination comprises at least one agent that oxidizes GSH, or a precursor thereof, and at least one agent that inhibits the GR enzyme.

13. A method according to claim 12 wherein said least one agent that oxidizes
5 GSH or a precursor thereof is disulfiram, hydrogen peroxide, a precursor thereof selected from the group consisting of ascorbic acid and dopamine, α -lipoic acid, oxidized low density lipoproteins (ox-LDLs), and a quinone selected from the group consisting of duroquinone, an ubiquinone, and β -lapachone, and said at least one agent that inhibits the GR enzyme is carmustine.

10 14. A method according to claim 5 wherein said synergistic combination comprises at least one agent that forms an adduct or conjugate with GSH, or a precursor thereof, and at least one agent that inhibits the GCS enzyme, with the exclusion of the combination of As_2O_3 with BSO.

15 15. A method according to claim 5 wherein said synergistic combination comprises at least one agent that forms an adduct or conjugate with GSH, or a precursor thereof, and at least one agent that inhibits the GR enzyme

16. A method according to claim 5 wherein said synergistic combination is administered continuously to said patient for a period of time within the range of from about 15 to about 75 hours.